B2 2. Description of Related Art.

Kindly amend the paragraph appearing at page 1, lines 10-14, such that it reads the following:

B3 Post-operative treatment of prostate and mammary carcinomas with agonists of gonadotropin releasing hormone (GnRH, in the literature also referred to as luteinizing hormone releasing hormone; LH-RH) is a standard treatment; cf. Gonzalez-Barcena et al., 1994, The Prostate 24, 84-92; Emons and Schally, 1994, Human Reproduction Update 9, No. 7, 1364-1379.

Kindly amend the paragraph appearing at page 1, lines 15-18, such that it reads the following:

B4 Thus, in various steroid hormone (sexual hormone) dependent malignant tumors, such as mammary carcinoma, prostate carcinoma, ovarian carcinoma, and endometrial carcinoma, a double effect has been observed in clinical studies upon treatment with GnRH agonists:

Kindly amend the paragraph appearing at page 1, lines 24-27, such that it reads the following:

B5 The above-mentioned indirect effect due to steroid hormone dependence is known since decades for the prostate and the mammary carcinoma; cf. Gonzalez-Barcena et al., 1994, The Prostate 24, 84-92; Jonat et al., 1995, European Journal of Cancer 31A, 137-142.

Kindly amend the sentence appearing at page 1, lines 28-30, such that it reads the following:

B6 The direct anti-proliferative effect of GnRH agonists and GnRH antagonists on e.g. prostate carcinomas, mammary carcinomas, and ovarian carcinomas has been confirmed by clinical studies.

Kindly amend the paragraph appearing at page 2, lines 12, to page 3, line 9, such that it reads the following:

Research with cell culture has revealed that GnRH receptors are present on human primary liver cell carcinomas and pancreas adenocarcinomas. In addition, the beginning of a biochemical metabolization with respect to cleavage of GnRH between tyrosine 5 and glycine 6 in rat glioma and rat neuroblastoma has been described; cf. Tao et al., 1991, Neuropeptides 20, 125-131. Ligand binding of GnRH to the GnRH receptor and its signal transduction, however, take place in a different way, namely at the eighth amino acid of GnRH, arginine, and this exclusively occurs in the case of an intact conformation of the GnRH molecule and its amino acid side chains (Naor, Z., Schacham, Sh., Harris, D., Seger, R., and Riess, N., 1995, Signal Transduction of the Gonadotropin Releasing Hormone (GnRH) Receptor: Cross-Talk of Calcium, Protein Kinase C (PKC), and Arachidonic Acid. Cellular and Molecular Neurobiology, vol. 15, 527-545). In normal rat adenohypophysis where GnRH receptors reside, GnRH leads to an increased camp production, however, it is still unclear whether this is a direct or an indirect effect (paracrine interaction). For the function of the GnRH receptor in rat including secretion of LH as well as an increased production of LH stimulated by GnRH, the biochemical metabolization of GnRH, e.g. by means of cAMP, plays only an indirect role (Abdilnour, G., and Bourne, G.A., 1995, Adenosine 3'5'-cyclic mono-phosphate and the self-priming effect of gonadotropin-releasing hormone. Molecular and Cellular Endocrinology, 107, 1-7). Naturally, there were found GnRH receptors on human gonadotropin producing pituitary adenomas (Alexander, J.P., and Klibanski, A., Gonadotropin-releasing Hormone Receptor mRNA Expression by Human Pituitary Tumors In Vitro, 1994, Journal of Clinical Investigation, 93, 2332-2339). To treat the indication Pubertas praecox e.g. due to the GnRH-producing hamartoma of the hypothalamus, GnRH agonists were also employed in children in a symptomatic treatment of blocking gonadotropin-producing cells in the adenohypophysis (Mahachoklertwattana, P., Kaplan, S.L., Grumbach, M.M., The Luteinizing-Hormone-Releasing Hormone-Secreting Hypothalamic Hamartoma Is a Congenital Malformation: Natural History, 1993, Journal of Clinical Endocrinology and Metabolism, 77, 118-125).

On page 5, between lines 23 and 24, kindly insert the following section heading:

B8 SUMMARY OF THE INVENTION.

On page 6, following line 2, kindly insert the following section heading and text:

BRIEF DESCRIPTION OF THE DRAWINGS.

Figure 1 shows a plot of Intensity vs. Time for Antide.

B9

Figure 2 shows a plot of Intensity vs. Time for Triptorelin.

Figure 3 shows a plot of Intensity vs. Time for LHRH Hormone.

On page 6, following the newly inserted section entitled "Brief Description of the Drawings", kindly insert the following section heading:

B10 DETAILED DESCRIPTION OF THE INVENTION.

Kindly amend the paragraph appearing at page 10, line 29, to page 11, line 4, such that it reads the following:

B11 The above-mentioned GnRH agonists and GnRH antagonists may be administered in dosages approved for other treatments. There may also be used dosages established during dose finding studies for the use of similar materials (substances, medicaments) such as somatostatin analogues in pituitary adenoma, glioblastoma or pancreas adenocarcinoma, or for phase II studies with GnRH analogues (agonists or antagonists) for other indications, e.g. mammary carcinoma, prostate carcinoma or ovarian carcinoma.

Kindly amend the paragraph appearing at page 11, lines 13-22, such that it reads the following:

For the first time, the GnRH receptor concentration in cell membranes of human brain or nervous system tumor cells, i.e. the GnRH receptors on the membrane which are effective in vitro have been determined using a radio receptor assay. With the method according to the invention, the biological activity or specifically the active GnRH receptors, respectively, are determined. For this purpose, radiolabeled BUSERELIN, a GnRH agonist, is used as a marker binding specifically to GnRH receptors. Based on radioactive counts of bound BUSERELIN the GnRH receptor concentration may be determined. This detection has already been used for other tumors such as mammary carcinoma and the like. The method used according to the present invention measures the GnRH receptor concentration on cell membrane extracts of fresh human tumor tissue.

B 12

Kindly amend the paragraph appearing at page 12, line 24, to page 13, line 5, such that it reads the following:

The exact mechanism of action of GnRH agonists or GnRH antagonists on tumors is unknown. For the tumor types known so far having active GnRH receptors such as mammary carcinoma, prostate carcinoma and ovarian carcinoma, a locally regulatory autocrine-paracrine system has been proposed in the literature; cf. Irmer et al., 1995, Cancer Research 55, 817-822. For the tumors mentioned, anti-proliferative activities of GnRH agonists or GnRH antagonists have been described in the literature, both in vitro (Palyi et al., 1996, Cancer Detection and Prevention, 20, 146-152; Irmer et al., 1995, Cancer Research, 55, 817-822; Pati et al., 1995, Endocrinology, 136, 75-84) and in vivo or clinically, respectively; cf. Gonzalez-Barcena et al., 1994, The prostate 24, 84-92; Jonat et al., 1995, European J. of Cancer, 31A, 137-142; Emons and Schally, 1994, Human Reproduction Update 9, No. 7, 1364-1379; wherein this anti-proliferative activity goes beyond the anti-proliferative effect to be expected of reversible "chemical castration" by GnRH agonists.

B 13
